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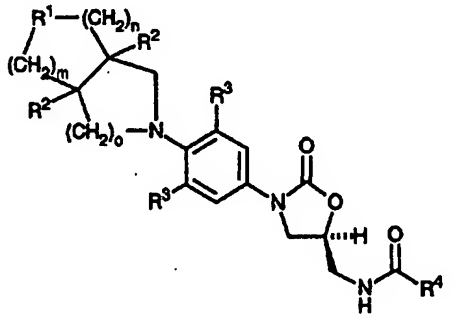
(54) Title: SPIROCYCLIC AND BICYCLIC DIAZINYL AND CARBAZINYL OXAZOLIDINONES

(57) Abstract

A compound of structural Formula (I or II) useful for treating microbial infections in humans or other warm-blooded animals, or pharmaceutically acceptable salts thereof as defined herein.



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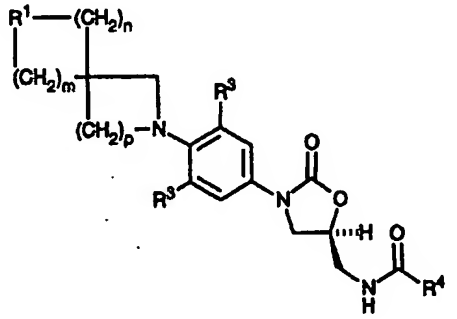

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SPIROCYCLIC AND BICYCLIC DIAZINYL AND CARBAZINYL OXAZOLIDINONES

Background of the Invention

The subject invention discloses new and useful oxazolidinones having a spirocyclic or bicyclic diazinyl or carbazinyl moiety. The compounds are useful antimicrobial agents effective against a number of human and veterinary pathogens, including gram-positive aerobic bacteria such as multiply-resistant staphylococci, streptococci and enterococci as well as anerobic organisms such as Bacteroides spp. and Clostridia spp. species, and acid-fast organisms such as *Mycobacterium tuberculosis* and other mycobacterial species.

Information Disclosure

The present compounds are related by their phenyloxazolidinone ring structure to those disclosed in the publications below except that the subject compounds have a spirocyclic or bicyclic diazinyl or carbazinyl moiety. The instant compounds have useful antibacterial activity.

PCT/US94/08904 application discloses oxazolidinone antibacterial compounds having either a morpholine or thiomorpholine substituent.

PCT/US93/03570 application discloses oxazolidinones containing a substituted diazine moiety and their uses as antimicrobials.

PCT/US92/08267 application discloses substituted aryl and heteroaryl-phenyl-oxazolidinones useful as antibacterial agents.

PCT/US89/03548 application discloses 5'indolinyl-5ß-amidomethyloxazolidinones, 3-(fused-ring substituted)phenyl-5ß-amidomethyloxazolidinones, and 3-(nitrogen substituted)phenyl-5ß-amidomethyloxazolidinones which are useful as antibacterial agents.

Other references disclosing various oxazolidinones include US Patent 4,801,600, 4,921,869, Gregory W. A., et al., J. Med. Chem., 32, 1673-81 (1989); Gregory W. A., et al., J. Med. Chem., 33, 2569-78 (1990); Wang C., et al., Tetrahedron, 45, 1323-26 (1989); and Brittelli, et al., J. Med. Chem., 35, 1156 (1992).

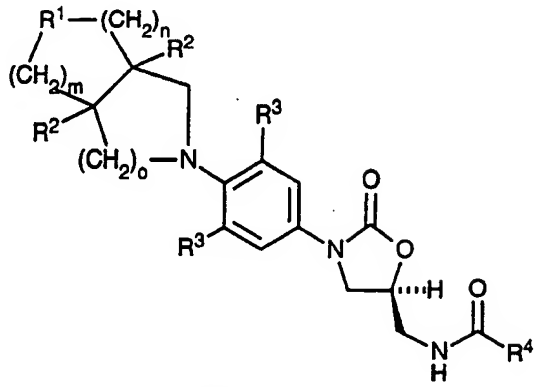
European Patent Publication 352,781 discloses phenyl and pyridyl substituted phenyl oxazolidinones.

European Patent Publication 316,594 discloses 3-substituted styryl oxazolidinones.

European Patent Publication 312,000 discloses phenylmethyl and pyridinylmethyl substituted phenyl oxazolidinones.

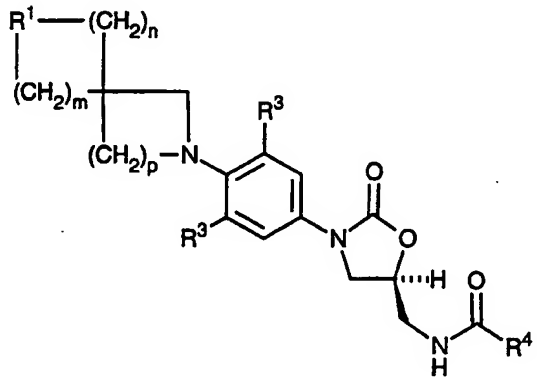
Summary of the Invention

In one aspect the subject invention is a compound of structural Formula I:



Formula I

In another aspect the subject invention is composed of structural Formula II:



Formula II

or pharmaceutically acceptable salts thereof wherein:

R^1 is (a) NR^5,

(b) CR^6R^7;

R^2 is independently H or CH_3;

R^3 is independently H, F, Cl or methoxy;

R^4 is (a) hydrogen,

(b) C_1-C_8 alkyl (optionally substituted with one or more of the following: F, Cl, hydroxy, C_1-C_8 alkoxy, C_1-C_8 acyloxy),

(c) C_3-C_6 cycloalkyl,

(d) amino,

(e) C_1-C_8 alkylamino,

(f) C_1-C_8 dialkylamino,

(g) C_1-C_8 alkoxy;

R^5 is (a) H,

(b) C_{1-6} alkyl (optionally substituted with one or more of the following: Cl, F, CN, OH, C_{1-4} alkoxy, amino, hydroxylamino, alkoxylamino, C_{1-4} acyloxy, C_{1-4} alkylsulfenyl, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, aminosulfonyl, C_{1-4} alkylaminosulfonyl, C_{1-4} dialkylaminosulfonyl, 4-morpholinylsulfonyl, phenyl (optionally substituted with one or more of F, Cl, CN, OH, C_1-C_4alkoxy), 5-isoxazolyl, ethenyloxy, ethynyl),

(c) C_{1-6} acyl (optionally substituted with one or more of the following: Cl, F, OH, SH, C_{1-4} alkoxy, naphthalenoxy and phenoxy (optionally substituted with one or more of the following: Cl, F, OH, C_1-C_4alkoxy, amino, C_1-C_4acylamino, C_1-C_4alkyl), amino, C_1-C_4acylamino, hydroxylamino, alkoxylamino, C_{1-4} acyloxy, phenyl, C_1-C_4alkylcarbonyl, C_1-C_4alkylamino, C_1-C_4dialkylamino, C_1-C_4hydroxyacyloxy, C_1-C_4alkylsulfenyl, phthalimido, maleimido, succinimido),

(d) C_{1-6} alkylsulfonyl (optionally substituted with one or more of the following: Cl, F, OH, C_{1-4} alkoxy, amino, hydroxylamino, alkoxylamino, C_{1-4} acyloxy, phenyl),

(e) arylsulfonyl (optionally substituted with one or more of the following: F, Cl, OCH_3, OH or C_{1-4} alkyl),

(f) C_{1-6} alkoxycarbonyl (optionally substituted with one or more of the following: Cl, F, OH, C_{1-4} alkoxy, C_{1-4} acyloxy, phenyl),

(g) aminocarbonyl, C_{1-6} alkylaminocarbonyl or C_{1-6} dialkylaminocarbonyl (where the alkyl groups are optionally substituted with one or more of the following: Cl, F, OH, C_{1-4} alkoxy, phenyl),

(h) five- and six-membered heterocycles, especially 2-oxazolyl, 2-thiazolyl, 3-isoxazolyl, 3-isothiazolyl and dihydro derivatives of these ring systems (all optionally substituted with one or more of the following: Cl, F, OH, amino, C_{1-4}acylamino, C_{1-4} alkylsulfonylamino, C_{1-4} alkoxycarbonylamino, C_{1-4} alkoxy, C_{1-4} acyloxy, C_{1-4}alkyl which can be substituted with F, OH or C_{1-4} alkoxy,

(i) C_3-C_6 cycloalkylcarbonyl (optionally substituted with one or more of the following: F, Cl, OH, C_1-C_4alkoxy, CN),

(j) benzoyl (optionally substituted with one or more of the following: F, Cl, OH, C_1-C_4alkoxy, C_1-C_4alkyl, amino, C_1-C_4acylamino),

(k) pyrrolylcarbonyl (optionally substituted with one or more of C_1-C_4alkyl),

(l) C_1-C_2 acyloxyacetyl (acyl optionally substituted with the following: amino, C_1-C_4alkylamino, C_1-C_4dialkylamino, 4-morpholino, 4-aminophenyl, 4-(dialkylamino)phenyl, 4-(glycylamino)phenyl);

R^6 is (a) H,

(b) OH,

(c) C_{1-6} alkoxy,

(d) amino, C_{1-6} alkylamino, C_{1-6} dialkylamino, hydroxylamino, or C_{1-2} alkoxylamino (all of which can be optionally substituted on the nitrogen with: C_{1-6} acyl optionally substituted with one-two of Cl or OH, C_{1-6} alkylsulfonyl optionally substituted with one-two of Cl or OH, C_{1-6} alkoxycarbonyl),

(e) Cl or F;

R^7 is (a) H,

(b) C_{1-6} alkyl (optionally substituted with one or more of the following: Cl, F, CN, OH, C_{1-4} alkoxy, C_{1-4} acyloxy, amino),

(c) CN,

(d) phenyl (optionally substituted with one or more of the following: Cl, F, OH, C_{1-4} alkoxy); or

R^6 and R^7 taken together are (a) carbonyl or thiocarbonyl group,

(b) ethylene ketal (-OCH_2CH_2O-), propylene ketal (-$OCH_2CH_2CH_2O$-), ethylene thioketal (-SCH_2CH_2S-), propylene thioketal (-$SCH_2CH_2CH_2S$-), dimethyl ketal, diethyl ketal, dimethyl thioketal and diethyl thioketal,

(c) oxime (optionally substituted with H, C_{1-6} alkyl (optionally substituted with Cl, F or C_{1-4} alkoxy), C_{1-6} acyl (optionally substituted with one or more of the following: Cl, F, OH, C_{1-4} alkoxy, C_{1-4} acyloxy),

(d) hydrazone (optionally substituted with H, C_{1-6} alkyl (optionally substituted with one or more Cl, F, OH, C_{1-4} alkoxy, C_{1-4} acyloxy, phenyl, C_{1-6} acyl (optionally substituted with one or more of Cl, F, OH, C_{1-4} alkoxy, C_{1-4} acyloxy, phenyl), C_{1-6} alkoxycarbonyl (optionally substituted with one or more of the following: Cl, F, OH,

C_{1-4} alkoxy, C_{1-4} acyloxy, phenyl), C_{1-6} alkylsulfonyl,

(e) imine (optionally substituted with H or a C_{1-6} alkyl (optionally substituted with Cl, F, OH, C_{1-4} alkoxy, C_{1-4} acyloxy, phenyl),

(f) carbon-carbon double bond (optionally substituted with H, C_{1-4} alkoxycarbonyl, C_{1-4} alkyl (optionally substiuted with Cl, F, OH, C_{1-4} alkoxy, phenyl);

m is 0-2;

n is 1-3;

o is 0-3; and

p is 1-3.

In another aspect, the subject invention is directed toward a method for treating microbial infections in humans or other warm-blooded animals by administering to a patient in need thereof an effective amount of a compound of Formula I or II as described above. The compound can be administered in a pharmaceutical composition either orally, parenterally or topically. Preferably the compound is administered orally or parenterally in an amount of from about 0.1 to about 100 mg/kg of body weight/day, more preferably, from about 3.0 to about 50 mg/kg of body weight/day.

Detailed Description of the Invention

The present invention discloses novel spirocyclic and fused bicyclic diazinyl and carbazinyl oxazolidinones of structural Formula I and II as described above. The compounds are useful antimicrobial agents, effective against a number of human and veterinary pathogens, particularly aerobic gram-positive bacteria, including multiply-resistant staphylococci, streptococci and enterococci, as well as anaerobic organisms such as bacteroides and clostridia species, and acid-fast bacteria such as as *Mycobacterium tuberculosis* and other mycobacterial species.

The R groups are as set forth above. As used herein the term C_{n-m} is inclusive such that a compound of C_{1-8} would include compounds of one to 8 carbons and their isomeric forms. The various carbon moieties are defined as follows: Alkyl refers to an aliphatic hydrocarbon radical and includes branched or unbranched forms such as methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, i-pentyl, neo-pentyl, n-hexyl, i-hexyl, n-heptyl, i-heptyl and n-octyl. Acyl refers to those having one to six carbon atoms such as formyl, acetyl, propionyl, etc. and their isomeric forms.

The R^3 substituents are preferably both fluorine and, more preferably,

fluorine and hydrogen.

The R^4 substituent is preferably hydrogen, methyl, difluoromethyl, dichloromethyl, hydroxymethyl or methoxy. More preferably R^4 is methoxy, difluoromethyl, dichloromethyl or methyl. It is most preferred that R^4 is methyl.

The R^5 substituent is preferably hydroxyacetyl.

The preferred absolute configuration at C-5 of the oxazolidinone ring of compounds claimed in this invention is as represented in the structures of Formula I and II. This absolute configuration is called (*S*) under the Cahn-Ingold-Prelog nomenclature system. It is this (*S*)-enantiomer which is pharmacologically active. The racemic mixture is useful in the same way and for the same purpose as the pure (*S*)-enantiomer; the difference is that twice as much racemic material must be used to produce the same antibacterial effect. It will be apparent to one skilled in the art that when a chiral center is present in the diazinyl or carbazinyl fragment of compounds of structural Formula I and II, then diastereomers are possible. These diastereomers, in racemic and enantiomerically enriched forms, are also within the scope of the compounds of Formula I and II of the invention.

Both organic and inorganic acids can be employed to form non-toxic pharmaceutically acceptable acid addition salts of the compounds of this invention, where applicable. Illustrative acids are sulfuric, nitric, phosphoric, hydrochloric, citric, acetic, lactic, tartaric, pamoic, ethanedisulfonic, sulfamic, succinic, cyclohexylsulfamic, fumaric, maleic, and benzoic acid. These salts are readily prepared by methods known in the art.

Pharmaceutical compositions of this invention may be prepared by combining the compounds of Formula I or II with a solid or liquid pharmaceutically acceptable carrier and, optionally, with pharmaceutically acceptable adjuvants and excipients employing standard and conventional techniques. Such pharmaceutical compositions can then be used in treating microbial infections in humans or other warm-blooded animals (patients) by various routes of administration in an effective amount or therapeutically effective amount. Typical amounts can be from about 0.1 to about 100 mg/kg of body weight/day, more preferably, from about 3.0 to about 50 mg/kg of body weight/day.

Solid form compositions include powders, tablets, dispersible granules, capsules, cachets and suppositories. A solid carrier can be at least one substance which may also function as a diluent, flavoring agent, solubilizer, lubricant, suspending agent, binder, tablet disintegrating agent, and encapsulating agent. Inert solid carriers include magnesium carbonate, magnesium stearate, talc, sugar,

lactose, pectin, dextrin, starch, gelatin, cellulosic materials, low melting wax, cocoa butter, and the like. Liquid form compositions include solutions, suspensions and emulsions. For example, there may be provided solutions of the compounds of this invention dissolved in water and water-propylene glycol and water-polyethylene glycol systems, optionally containing suitable conventional coloring agents, flavoring agents, stabilizers and thickening agents.

Preferably, the pharmaceutical composition is provided employing conventional techniques in unit dosage form containing effective or appropriate amounts of the active component, that is, the compound of Formula I according to this invention.

The quantity of active component, that is the compound of Formula I or II according to this invention, in the pharmaceutical composition and unit dosage form thereof may be varied or adjusted widely depending upon the particular application, the potency of the particular compound, the desired concentration. Generally, the quantity of active component will range between 0.5% to 90% by weight of the composition.

In therapeutic use for treating, or combatting, bacterial infections in warm-blooded animals, the compounds or pharmaceutical compositions thereof will be administered orally and/or parenterally at a dosage to obtain and maintain a concentration, that is, an amount, or blood-level of active component in the animal undergoing treatment which will be antibacterially effective. Generally, such antibacterially effective amount of dosage of active component will be in the range of about 0.1 to about 100, more preferably about 3.0 to about 50 mg/kg of body weight/day. It is to be understood that the dosages may vary depending upon the requirements of the patient, the severity of the bacterial infection being treated, and the particular compound being used. Also, it is to be understood that the initial dosage administered may be increased beyond the above upper level in order to rapidly achieve the desired blood-level or the initial dosage may be smaller than the optimum and the daily dosage may be progressively increased during the course of treatment depending on the particular situation. If desired, the daily dose may also be divided into multiple doses for administration, e.g., two to four times per day.

The compounds of Formula I or II according to this invention are administered parenterally, i.e., by injection, for example, by intravenous injection or by other parenteral routes of administration. Pharmaceutical compositions for parenteral administration will generally contain a pharmaceutically acceptable amount of the compound according to Formula I or II as a soluble salt (acid

addition salt or base salt) dissolved in a pharmaceutically acceptable liquid carrier such as, for example, water-for-injection and a buffer to provide a suitably buffered isotonic solution, for example, having a pH of about 3-7. Suitable buffering agents include, for example, trisodium orthophosphate, sodium bicarbonate, sodium citrate, N-methylglucamine, L(+)-lysine and L(+)-arginine to name but a few representative buffering agents. The compound according to Formula I or II generally will be dissolved in the carrier in an amount sufficient to provide a pharmaceutically acceptable injectable concentration in the range of about 1 mg/ml to about 400 mg/ml of solution. The resulting liquid pharmaceutical composition will be administered so as to obtain the above-mentioned antibacterially effective amount of dosage.

A method of preparation of oxazolidinones of Formula I and II in enantiomerically pure form is depicted in Charts I-VI.

As shown in Chart I, fused bicyclic diazines and carbazines of structure **1** are known in the literature. EP 0 350 733 A2. Dave, P. R.; Forohar, F.; Axenrod, T.; Qi, L.; Watnick, C.; Yazdekhasti, H. *Tetrahedron Lett.* **1994**, *35*, 8965. Jacquet, J.-P.; Bouzard, D.; Kiechel, J.-R.; Remuzon, P. *Tetrahedron Lett.* **1991**, *32*, 1565. JP 8956 673. *Chem. Abstr.* **1989**, *111*, 153779w. Loftus, P.; *et al. J. Heterocycl. Chem.* **1983**, *20*, 321. Gobeaux, B.; Ghosez, L. *Heterocycles* **1989**, *28*, 29. Xu, W.; Zhang, X.-M.; Mariano, P. S. *J. Am. Chem. Soc.* **1991**, *113*, 8863. In addition, spirocyclic diazines and carbazines of structure **2** are also known substances. Culbertson, T. P.; Sanchez, J. P.; Gambino, L.; Sesnie, J. A. *J. Med. Chem.* **1990**, *33*, 2270. Domagala, J. M.; *et al.* U.S. Patent 4 638 067, 1987. Xu, W.; Zhang, X.-M.; Mariano, P. S. *J. Am. Chem. Soc.* **1991**, *113*, 8863.

Charts II-VI outline the synthesis of oxazolidinone antibacterial agents of structural Formula I and II from diazines or carbazines **1** and **2**.

As shown in Chart II, diazine or carbazine **1** is reacted with a functionalized nitrobenzene **3** (X = halogen or trifluoromethanesulfonate) in the presence of a suitable base/solvent combination, for example dibasic potassium phosphate in dimethyl sulfoxide or *N,N*-diisopropylethylamine in acetonitrile or THF, and at a suitable temperature, typically ambient temperature to 70°C, to afford the adduct **4**. It will be apparent to one skilled in the art that the R^1 residue of compound **1** might require the presence of a suitable protecting group. For example, in the diazine case, where R^1 is nitrogen, the benzyl protecting group was found to be effective at blocking this position. Alternatively, in the case of carbazine variants (R^1 =

functionalized carbon) sensitive groups such as a hydroxyl group can be protected as their *tert*-butyldimethylsilyl ethers. In the case where R^1 is a carbonyl, prior conversion to a ketal protects this functional group from subsequent chemical conversions. It will be apparent to those skilled in the art that these protecting groups are merely representative and that alternative protecting groups, such as those described in Greene, T. W.; Wuts, P. G. M. "Protective Groups in Organic Synthesis", 2nd ed.; John Wiley & Sons: New York, 1991, can be employed. The nitro group of **4** is then reduced by catalytic hydrogenation in the presence of a suitable catalyst, such as 10% palladium/carbon or W-2 Raney nickel, and in an appropriate solvent, for example THF/H_2O. When this latter solvent system is utilized, the reaction mixture is first filtered to remove the catalyst and the filtrate containing the intermediate aniline is then treated with, for example, sodium bicarbonate and benzyl or methyl chloroformate to give the corresponding benzyl (R = CH_2Ph) or methyl (R = CH_3) urethane derivatives **5**. When R^1 is a benzylamino residue, the benzyl group is lost under the hydrogenation conditions and is replaced, for example, with a Cbz group during the subsequent urethane forming reaction. The urethanes **5** are then deprotonated with a suitable base such as *n*-butyllithium (*n*-BuLi), lithium diisopropylamide (LDA) or lithium bis(trimethylsilyl)amide, in a suitable solvent such as tetrahydrofuran (THF) and at a suitable temperature such as -78 to -60°C to give a lithiated intermediate which is then treated with commercially available (-)-(*R*)-glycidyl butyrate. Warming to ambient temperature then directly affords the 5-(hydroxymethyl)oxazolidinones **6** in enantiomerically enriched form.

As shown in Chart III, compound **6** is then converted to the corresponding mesylate **7** (R = methyl) or aryl sulfonate **7** (R = $ArSO_2$, for example *p*-toluenesulfonyl) by the action of, for example, methanesulfonyl chloride/pyridine or methanesulfonyl chloride/triethylamine/dichloromethane or *p*-toluenesufonyl chloride/pyridine. The resultant sulfonate derivative **7** is then reacted with an azide source such as sodium or potassium azide in an aprotic solvent such as *N,N*-dimethylformamide (DMF) or 1-methyl-2-pyrrolidinone optionally in the presence of a catalyst such as 18-crown-6 at a temperature of 50-90 °C to afford the azide **8**. The azide is then reduced by hydrogenation with palladium on carbon or a platinum catalyst in an appropriate solvent such as ethyl acetate or methanol to give the corresponding amine **9**. Alternatively, the azide **8** can be reduced by treatment with a trivalent phosphorus compound such as triphenylphosphine in a suitable solvent such as tetrahydrofuran followed by the addition of water. The intermediate amine

9 may also be prepared by treatment of the phthalimide derivative **10** (obtained by reacting sulfonate **7** with potassium phthalimide in a suitable solvent, for example, acetonitrile at reflux temperature) with methylamine in ethanol/H_2O at reflux temperature. Alternatively, the amine **9** may be prepared directly from the mesylate **7** by ammonolysis in a solvent system consisting of H_2O/ispropanol/THF in a sealed reaction vessel immersed in a 70-95 °C oil bath. The amine **9** is then acylated by reactions known to those skilled in the art to give oxazolidinones of structure **11**. For example, the amine can be reacted with an acid chloride or anhydride in a basic solvent such as pyridine at a temperature ranging from -30 to 30 °C to provide the acylated compound **11** (R^4 = optionally substituted alkyl). It will be apparent to one skilled in the art that other carbonyl groups within the scope of this invention can be readily appended to the amine **9** by standard acylation techniques, for example those highlighted in March, J. "Advanced Organic Chemistry", 3rd ed.; John Wiley & Sons: New York, 1985; p 370-375, to give additional examples of **11**. The oxazolidinones **11** are examples of structural Formula I, which are the subject of this invention.

As shown in Charts IV and V, selected examples of the fused bicyclic diazine and carbazine containing oxazolidinones **11**, themselves antibacterial agents of structural Formula I, can be further elaborated to additional compounds of Formula I.

Compound **12** (see Chart IV), efficiently obtained by catalytic hydrogenolysis of the corresponding Cbz protected derivative **11** (R^1 = CbzN), can be N-alkylated by procedures known to one skilled in the art, including treatment of **12** with alkyl halides or tosylates in the presence of a suitable base, to furnish compounds **13**. Alternatively, selected alkyl groups can be appended on the nitrogen of **12** by a reductive alkylation procedure as described in March, J. "Advanced Organic Chemistry", 4th ed.; John Wiley & Sons: New York, 1992; p 898-900. Compound **12** can also be converted to various acylated derivatives **14** by treatment of **12** with various carbonyl derivatives, such as acid chlorides, anhydrides and the like, in the presence of appropriate bases, and in suitable solvents known to one skilled in the art. Similarly, sulfonamide derivatives **15** are prepared by reacting **12** with alkyl- and arylsulfonyl chlorides in the presence of suitable amine bases and in appropriate solvents known to one skilled in the art. Urethanes **16** are prepared from compound **12** through the action of chloroformates and the like in the presence of appropriate bases and in suitable solvent systems known to one skilled in the art.

The above discussion should be considered merely representative in nature, since other derivatives of **12** are possible, for example the reaction of **12** with an isocyanate to give ureas **14** (R = NHY, where Y is an optionally substituted alkyl or phenyl group). Compounds **12-16** are fused bicyclic diazine examples of structural Formula I, which are the subject of this invention.

Compound **17** (see Chart V), readily obtained from ketal **11** [R^1 = $C(OCH_2CH_2O)$] by acidic hydrolysis, for example with *p*-toluenesulfonic acid in acetone/water, can be further elaborated to additional examples of structural Formula I. For example, various hydrazone derivatives **18** can be prepared by reacting **17** with hydrazines, as described in Greene, T. W.; Wuts, P. G. M. "Protective Groups in Organic Synthesis", 2nd ed.; John Wiley & Sons: New York, 1991, p 212-213 and March, J. "Advanced Organic Chemistry", 4th ed.; John Wiley & Sons: New York, 1992; p 904-905. Oximes **19** are readily prepared by reacting **17** with, for example, hydroxylamine hydrochloride or methoxylamine hydrochloride in the presence of a suitable base, such as pyridine, and in an appropriate solvent, for instance methanol, at ambient temperature. Imines **20** are synthesized by treating **17** with primary amines, as described in March, J. "Advanced Organic Chemistry", 4th ed.; John Wiley & Sons: New York, 1992; p 896-897. Olefinic derivatives **21** are prepared by reacting **17** with various olefinating reagents, such as phosphorus ylides and the like, which are known to one skilled in the art. Representative examples are described in March, J. "Advanced Organic Chemistry", 4th ed.; John Wiley & Sons: New York, 1992; p 956-963. The ketone moiety of **17** is amenable to further modification. Reaction of **17** with Lawesson's reagent or alternative reagents, as described in March, J. "Advanced Organic Chemistry", 4th ed.; John Wiley & Sons: New York, 1992; p 893-894, provides the corresponding thioketone **22**. It will be apparent to one skilled in the art that further transformations of **17-22** are possible. For example, catalytic hydrogenation conditions or borane-based reduction methods selectively reduce the ketone, oxime and olefin moieties, respectively, of **17**, **19** and **21** to give the corresponding hydroxy, amino and alkyl derivatives, respectively. Compound **17** can also be converted to corresponding cyclic and acyclic ketals and dithio ketals by reacting **17** with diols, dithiols, alcohols or thiols under conditions, for example, described in Greene, T. W.; Wuts, P. G. M. "Protective Groups in Organic Synthesis", 2nd ed.; John Wiley & Sons: New York, 1991, p 177-207. Compounds **17-22** and the above described derivatives represent examples of fused bicyclic carbazine oxazolidinone antibacterial agents, which are the subject of this

invention.

It will be apparent to those skilled in the art that the described synthetic procedures for making fused bicyclic diazinyl and carbazinyl oxazolidinone antibacterial agents are merely representative in nature and that alternative synthetic processes are known, for example some of those described in the cited references. It will also be apparent to those skilled in the art that the outlined synthetic process, with non-essential variations, is readily adaptable to the preparation of spirocyclic diazinyl and carbazinyl oxazolidinone antibacterial agents of structural Formula II, which are also the subject of this invention (see Chart VI).

EXAMPLE 1: (*S*)-N-[[3-[4-[*cis*-3-(carbobenzyloxy)-3,7-diazabicyclo[3.3.0]octan-7-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

Step 1: *cis*-3-benzyl-7-(2-fluoro-4-nitrophenyl)-3,7-diazabicyclo[3.3.0]octane

To a solution of *cis*-3-benzyl-3,7-diazabicyclo[3.3.0]octane (0.35 g, 1.73 mmol) in acetonitrile (10 mL) is added 3,4-difluoronitrobenzene (0.19 mL, 1.73 mmol) and potassium carbonate (0.60 g, 4.33 mmol) under a nitrogen atmosphere at ambient temperature. The reaction is stirred 15 hours, concentrated *in vacuo*, and diluted with ethyl acetate (100 mL). The organic phase is washed with water (3x20 mL) and saline (20 mL), dried over sodium sulfate, concentrated *in vacuo*, and chromatographed on silica gel (230-400 mesh, 100 mL), eluting with chloroform/methanol (99/1). The appropriate fractions are combined (R_f= 0.49, TLC, chloroform/methanol, 95/5) and concentrated *in vacuo* to give the title compound, NMR ($CDCl_3$) 7.94, 7.88, 7.29, 6.62, 3.73, 3.64, 3.44, 2.97, 2.75, 2.55.

Step 2: *cis*-3-(carbobenzyloxy)-7-[4-[(carbobenzyloxy)amino]-2-fluorophenyl]-3,7-diazabicyclo[3.3.0]octane

cis-3-Benzyl-7-(2-fluoro-4-nitrophenyl)-3,7-diazabicyclo[3.3.0]octane (9.11 g, 26.71 mmol), THF (100 mL), and methanol (50 mL) are combined with 10% palladium on carbon (6.67 g) and ammonium formate (16.83 g, 266.90 mmol) under nitrogen, heated to reflux for 2.5 hours, cooled to ambient temperature, stirred 15 hours, filtered through celite and concentrated *in vacuo* to give crude *cis*-3-(4-amino-2-fluorophenyl]-3,7-diazabicyclo[3.3.0]octane. *cis*-3-(4-Amino-2-fluorophenyl]-3,7-diazabicyclo[3.3.0]octane, water (100 mL), acetone (100 mL), and potassium carbonate (7.75 g, 56.07 mmol) are combined, cooled to 0°C, and benzyl chloroformate is added slowly. The reaction is warmed to ambient temperature,

stirred 15 hours, concentrated *in vacuo*, and diluted with ethyl acetate. The organic phase is washed with water (2x150 mL) and saline (150 mL), dried over sodium sulfate, concentrated *in vacuo*, and chromatographed on silica gel (230-400 mesh, 100 mL), eluting with hexane/ethyl acetate (80/20). The appropriate fractions are combined (R_f= 0.41, TLC, hexane/ethyl acetate, 50/50) and concentrated *in vacuo* to give the title compound, mp 121-122°C.

Step 3: (*R*)-[3-[4-[*cis*-3-(carbobenzyloxy)-3,7-diazabicyclo[3.3.0]octan-7-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methanol

To a flame dried flask cooled to -78°C and equipped with a nitrogen inlet is introduced *cis*-3-(carbobenzyloxy)-7-[4-[(carbobenzyloxy)amino]-2-fluorophenyl]-3,7-diazabicyclo[3.3.0]octane (7.25 g, 14.81 mmol), THF (100 mL), and 1.6 M butyl lithium (9.72 mL, 15.55 mmol). The reaction is stirred at -78°C for 1 hour before (*R*)-(-)-glycidyl butyrate (2.26 mL, 15.99 mmol) is added slowly and stirred for 2 hours at -78°C and 15 hours at ambient temperature. Saturated ammonium chloride (50 mL) is added and the aqueous phase is extracted with ethyl acetate (2x50 mL). The extracts are combined, washed with saline (50 mL), dried over sodium sulfate, concentrated *in vacuo*, and chromatographed on silica gel (230-400 mesh, 100 mL), eluting with chloroform/methanol (99/1). The appropriate fractions are combined (R_f= 0.13, TLC, chloroform/methanol, 95/5) and concentrated *in vacuo* to give the title compound, mp 168-171°C.

Step 4: (*S*)-N-[[3-[4-[*cis*-3-(Carbobenzyloxy)-3,7-diazabicyclo[3.3.0]octan-7-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

To a flame dried flask equipped with a nitrogen inlet is introduced (*R*)-[3-[4-[*cis*-3-(carbobenzyloxy)-3,7-diazabicyclo[3.3.0]octan-7-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methanol (1.75 g, 3.84 mmol) and methylene chloride (100 mL) cooled to 0°C. Triethylamine (0.80 mL, 5.76 mmol) and methanesulfonyl chloride are added, stirred at 0°C for 2 hours, and warmed to ambient temperature for 1 hour. The reaction is washed with water (30 mL), saturated sodium bicarbonate (30 mL), and saline (30 mL), dried over sodium sulfate, and concentrated *in vacuo* to give the crude (*R*)-[[3-[4-[*cis*-3-(carbobenzyloxy)-3,7-diazabicyclo[3.3.0]octan-7-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]methanesulfonate. (*R*)-[[3-[4-[*cis*-3-(Carbobenzyloxy)-3,7-diazabicyclo[3.3.0]octan-7-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]methanesulfonate is combined in a resealable tube with THF (5 mL), isopropanol (5 mL), and concentrated ammonium hydroxide (10 mL) and

heated to 95°C for 10 hours. The reaction is diluted with methylene chloride (50 mL) and washed with saline (30 mL), dried over sodium sulfate, concentrated *in vacuo* to give (*S*)-[[3-[4-[*cis*-3-(carbobenzyloxy)-3,7-diazabicyclo[3.3.0]octan-7-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]amine. The crude (*S*)-[[3-[4-[*cis*-3-(carbobenzyloxy)-3,7-diazabicyclo[3.3.0]octan-7-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]amine (1.67 g, 3.67 mmol) is dissolved in methylene chloride (20 mL), cooled to 0°C under nitrogen, pyridine (0.89 mL, 11.02 mmol) and acetic anhydride (0.43 mL, 4.59 mmol) are added, and the reaction is stirred 15 hours at ambient temperature. The reaction is diluted with methylene chloride (50 mL), washed with 1N HCl (25 mL), saturated sodium bicarbonate (25 mL), saline (25 mL), dried over sodium sulfate, concentrated *in vacuo*, and chromatographed on silica gel (230-400 mesh, 200 mL), eluting with chloroform/methanol (98/2). The appropriate fractions are combined (R_f= 0.15, TLC, chloroform/methanol, 95/5) and concentrated *in vacuo* to give the title compound, mp 165-168°C.

EXAMPLE 2: (*S*)-N-[[3-[3-fluoro-4-[*cis*-3-(benzyloxyacetyl)-3,7-diazabicyclo[3.3.0]octan-7-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

(*S*)-N-[[3-[4-[*cis*-3-(Carbobenzyloxy)-3,7-diazabicyclo[3.3.0]octan-7-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (150 mg, 0.30 mmol), methylene chloride (5 mL), and methanol (10 mL) are combined with 10% palladium on carbon (30 mg) and placed under a hydrogen atmosphere (balloon) for 15 hours. The reaction is filtered through celite and concentrated *in vacuo* to give crude (*S*)-N-[[3-[4-[*cis*-3,7-diazabicyclo[3.3.0]octan-7-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide. The crude amine is taken up in methylene chloride (15 mL), cooled to 0°C, and triethylamine (0.09 mL, 0.67 mmol) and benzyloxyacetyl chloride (0.06 mL, 0.40 mmol) are added. The reaction is warmed to ambient temperature, stirred 15 hours, and diluted with methylene chloride (100 mL). The organic phase is washed with water (2x50 mL) and saline (150 mL), dried over sodium sulfate, concentrated *in vacuo*, and chromatographed on silica gel (230-400 mesh, 100 mL), eluting with chloroform/methanol (95/5). The appropriate fractions are combined (R_f= 0.41, TLC, chloroform/methanol, 90/10) and concentrated *in vacuo* to give the title compound, mp 138-140°C.

EXAMPLE 3: (*S*)-N-[[3-[3-fluoro-4-[*cis*-3-(hydroxyacetyl)-3,7-diazabicyclo[3.3.0]octan-7-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

The (*S*)-N-[[3-[3-fluoro-4-[*cis*-3-(benzyloxyacetyl)-3,7-diazabicyclo[3.3.0]octan-7-

yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (110 mg, 0.22 mmol), methanol (25mL) and 10% palladium on carbon (100 mg) are combined and placed under 40 p.s.i. of hydrogen and shaken for 5 days. The reaction is filtered through celite, concentrated *in vacuo*, and chromatographed on silica gel (230-400 mesh, 100 mL), eluting with chloroform/methanol (95/5). The appropriate fractions are combined (R_f= 0.20, TLC, chloroform/methanol, 90/10) and concentrated *in vacuo* to give the title compound, mp 167-168°C.

EXAMPLE 4: (*S*)-N-[[3-[3-fluoro-4-[*cis*-3-(5-isoxazolinoyl)-3,7-diazabicyclo[3.3.0]octan-7-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

(*S*)-N-[[3-[4-[*cis*-3-(Carbobenzyloxy)-3,7-diazabicyclo[3.3.0]octan-7-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (150 mg, 0.30 mmol), methylene chloride (5 mL), and methanol (10 mL) are combined with 10% palladium on carbon (30 mg) and placed under a hydrogen atmosphere (balloon) for 15 hours. The reaction is filtered through celite and concentrated *in vacuo* to give crude (*S*)-N-[[3-[4-[*cis*-3,7-diazabicyclo[3.3.0]octan-7-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide. To the crude (*S*)-N-[[3-[4-[*cis*-3,7-diazabicyclo[3.3.0]octan-7-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (115 mg, 0.30 mmol) dissolved in pyridine (5 mL) at 0°C is added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (70 mg, 0.35 mmol), 4-dimethylaminopyridine (5 mg, 0.05 mmol), and isoxazole-5-carboxylic acid (40 mg, 0.35 mmol). The reaction is warmed to ambient temperature, stirred 15 hours, diluted with methylene chloride (30 mL). The organic phase is washed with 1N HCl (20 mL) and saline (20 mL), dried over sodium sulfate, concentrated *in vacuo*, and chromatographed on silica gel (230-400 mesh, 100 mL), eluting with chloroform/methanol (97/3). The appropriate fractions are combined (R_f= 0.16, TLC, chloroform/methanol, 95/5) and concentrated *in vacuo* to give the title compound, mp 172-175°C.

EXAMPLE 5: (*S*)-N-[[3-[3-fluoro-4-[*cis*-3-(2-indolylcarbonyl)-3,7-diazabicyclo[3.3.0]octan-7-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

Following the general procedure of EXAMPLE 4 and making noncritical variations but substituting indole-2-carboxylic acid (60 mg, 0.35 mmol) for isoxazole-5-carboxylic acid, the title compound is obtained, mp 211°C.

EXAMPLE 6: (*S*)-N-[[3-[3-fluoro-4-[*cis*-3-(carbomethoxy)-3,7-diazabicyclo[3.3.0]octan-

7-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

Following the general procedure of EXAMPLE 2 and making noncritical variations but substituting methyl chloroformate (80 mg, 0.80 mmol) for benzyloxyacetyl chloride, sodium bicarbonate (240 mg, 2.80 mmol) for triethylamine, and using acetone (5 mL) and water (5 mL) as solvent , the title compound is obtained, mp 128-132°C.

EXAMPLE 7: (*S*)-N-[[3-[3-fluoro-4-[*cis*-3-(formyl)-3,7-diazabicyclo[3.3.0]octan-7-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

Following the general procedure of EXAMPLE 4 and making noncritical variations but substituting formic acid (40 mg, 0.60 mmol) for isoxazole-5-carboxylic acid, the title compound is obtained, HRMS calcd for $C_{19}H_{23}N_4FO_4$: 390.1703. Found: 390.1709.

EXAMPLE 8: (*S*)-N-[[3-[3-fluoro-4-[*cis*-3-(acetyl)-3,7-diazabicyclo[3.3.0]octan-7-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

Following the general procedure of EXAMPLE 2 and making noncritical variations but substituting acetyl chloride (80 mg, 1.05 mmol) for benzyloxyacetyl chloride, the title compound is obtained, mp 168-170°C.

EXAMPLE 9: (*S*)-N-[[3-[4-[*cis*-3-(carbobenzyloxy)-3,7-diazabicyclo[3.3.0]octan-7-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

Step 1: *cis*-3-benzyl-7-(4-nitrophenyl)-3,7-diazabicyclo[3.3.0]octane

Following the general procedure of EXAMPLE 1, Step 1 and making noncritical variations but substituting 4-fluoronitrobenzene (8.16 g, 57.80 mmol) for 3,4-difluoronitrobenzene, the intermediate title compound is obtained, mp 121-123°C.

Step 2: *cis*-3-(carbobenzyloxy)-7-[4-[(carbobenzyloxy)amino]phenyl]-3,7-diazabicyclo[3.3.0]octane

Following the general procedure of EXAMPLE 1, Step 2 and making noncritical variations but substituting *cis*-3-benzyl-7-(4-nitrophenyl)-3,7-diazabicyclo[3.3.0]octane (1.00 g, 3.10 mmol) for *cis*-3-benzyl-7-(2-fluoro-4-nitrophenyl)-3,7-diazabicyclo[3.3.0]octane, the intermediate title compound is obtained, mp 145-146°C.

Step 3: (*R*)-[3-[4-[*cis*-3-(carbobenzyloxy)-3,7-diazabicyclo[3.3.0]octan-7-yl]phenyl]-2-oxo-5-oxazolidinyl]methanol

Following the general procedure of EXAMPLE 1, Step 3 and making noncritical variations but substituting *cis*-3-(carbobenzyloxy)-7-[4-[(carbobenzyloxy)amino]phenyl]-3,7-diazabicyclo[3.3.0]octane (575 mg, 1.22 mmol) for *cis*-3-(carbobenzyloxy)-7-[4-[(carbobenzyloxy)amino]-3-fluorophenyl]-3,7-diazabicyclo[3.3.0]octane, the intermediate title compound is obtained, mp 163-164°C.

Step 4: (*S*)-N-[[3-[4-[*cis*-3-(carbobenzyloxy)-3,7-diazabicyclo[3.3.0]octan-7-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

Following the general procedure of EXAMPLE 1, Step 4 and making noncritical variations but substituting (*R*)-[3-[4-[*cis*-3-(carbobenzyloxy)-3,7-diazabicyclo[3.3.0]octan-7-yl]phenyl]-2-oxo-5-oxazolidinyl]methanol (280 mg, 0.65 mmol) for (*R*)-[[3-[4-[*cis*-3-(carbobenzyloxy)-3,7-diazabicyclo[3.3.0]octan-7-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methanol, the title compound is obtained, mp 135-140°C.

EXAMPLE 10: (*S*)-N-[[3-[3-fluoro-4-[*cis*-2-(carbobenzyloxy)-2,8-diazabicyclo[4.3.0]nonan-8-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

Step 1:

(±)-*cis*-2,8-diazabicyclo[4.3.0]nonane (24.6 mmol) was dissolved into 30 mL of dry DMSO. The solution was treated with K_2HPO_4 (8.6 g, 49.2 mmol) followed by 3,4-difluoronitrobenzene (3.9 g, 24.6 mmol). The mixture became a bright orange color. The mixture was stirred for 20 hours at ambient temperature under N_2. After this time the mixture was poured into a separatory funnel along with $CHCl_3$. The solution was washed with H_2O and brine. The organic phase was separated and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated to give an orange oil that was purified by chromatography on silica gel eluting with a gradient of 1-5% MeOH/$CHCl_3$. This gave 4.2 g of product as an orange waxy solid. MP: 77-79°C.

Step 2:

The nitro aromatic product obtained in Step1 (1.5 g, 5.65 mmol) was dissolved into 50 mL of THF. The solution was treated with the catalyst 10% Pd/C under a stream of N_2. The mixture was degassed by evacuation and flushing with N_2 (3 times), followed by evacuation and flush with H_2 (3 times). The mixture was maintained at 35 psi of H_2 and was shaken on the parr. After 4 hours of reaction time TLC showed starting material was consumed. This solution was diluted with 50 mL of 1:1 acetone/H_2O and the mixture was cooled to 0°C. The reaction mixture

was treated with solid $NaHCO_3$ (1.4 g, 17.0 mmol) followed by benzyl chloroformate (2.0 g, 11.9 mmol). This mixture was left to stir overnight with warming to room temperature. After 16 hours the reaction mixture was diluted with CH_2Cl_2 and filtered through celite. The filtrate was poured into a separatory funnel along with H_2O. The mixture was shaken and the organic phase was separated, washed with brine followed by drying over anhydrous Na_2SO_4. The solution was filtered and concentrated to give a solid that was purified by chromatography on silica gel eluting with 5:1 hexane/EtOAc. Isolated 2.0 g of U-141248 as a yellow solid. This material was recystallyzed from 10% EtOAc/hexane to give a white solid. MP: 139-140°C.

Step 3:

The product of Step 2 (505 mg, 1.00 mmol) was dissolved into 10 mL of dry THF and the solution was cooled to -78°C. The solution was treated with *n*-BuLi (1.6 M soln. in hexanes; Aldrich; 656 µL, 1.05 mmol) via syringe. After 10 minutes (*R*)-glycidyl butyrate (151 mg, 1.05 mmol) was added and the mixture was left to stir overnight with warming to room temperature. After 14 hours the mixture was examined by TLC which showed the starting material was consumed. The reaction was poured into a separatory funnel along with EtOAc. The mixture was washed with saturated aqueous NH_4Cl and brine. The organic phase was separated and dried over anhydrous Na_2SO_4. Filtered and concentrated to give a residue that was purified by radial chromatography eluting with a gradient of 1-3% MeOH/$CHCl_3$. Isolated 294 mg of 5-(hydroxymethyl)oxazolidinone intermediate as a tan foam. MP: 71-73°C.

Step 4:

The alcohol obtained in Step3 (880 mg, 1.90 mmol) was dissolved into 15 mL of dry CH_2Cl_2 and the solution was cooled to 0°C. The solution was treated with Et_3N (336 mg, 3.32 mmol) and stirred for 5 minutes. Next solid 3-nitrobenzenesulfonyl chloride (NosylCl, 561 mg, 2.53 mmol) was added and the mixture was stored in the freezer overnight. After 15 hours TLC showed the starting alcohol was consumed with the formation of a new higher R_f product. The reaction was poured into a separatory funnel along with CH_2Cl_2. The solution was washed with 1.0 N aqueous HCl and saturated sodium bicarbonate. The organic phase was separated and dried over anhydrous Na_2SO_4. Filtered and concentrated to give 1.3 g of the nosylate as an orange foam. This material was used without purification.

Step 5:

The crude nosylate (1.9 mmol) was dissolved into 10 mL of CH_3CN and the solution was transfered to a resealable tube. The solution was diluted with 5 mL of isopropanol and 10 mL of 28% aqueous NH_4OH. The tube was sealed and heated to 65°C. After 15 hours the solution was cooled to ambient temperature and TLC showed that the nosylate was consumed. The reaction was poured into a separatory funnel along with CH_2Cl_2. The solution was washed with saturated aqueous $NaHCO_3$ and brine. The organic phase was separated and dried over anhydrous Na_2SO_4. Filtered and concentrated to give the crude amine as a foam. This material was dissolved into 20 mL of dry CH_2Cl_2 and the solution was cooled to 0°C. The reaction was treated with 500 µL of dry pyridine along with an excess of Ac_2O (200 µL). This mixture was left to stir overnight with warming to room temperature. After 18 hours the reaction mixture was poured into a separatory funnel along with CH_2Cl_2. The solution was washed with 1.0 N aqueous HCl and saturated aqueous $NaHCO_3$. The organic phase was separated and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated to give a tan foam that was purified on silica gel by radial chromatography eluting with 3% MeOH/$CHCl_3$. This provided 776 mg of the title compound as a tan foam (mixture of diastereomers). MP: 74-76°C. HRMS (EI) calcd for $C_{27}H_{31}FN_4O_5$ 510.2278, found 510.2278.

EXAMPLE 11: (*S*)-N-[[3-[3-fluoro-4-[*cis*-2-(carbomethoxy)-2,8-diazabicyclo[4.3.0]nonan-8-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

Step 1:

The starting material, EXAMPLE 10, (850 mg, 1.7 mmol) was dissolved into 20 mL of MeOH. The solution was treated with the catalyst 10% Pd/C (85 mg) under a stream of N_2. The parr bottle was evacuated and flushed with N_2 (3 times) followed by evacuation and flushed with H_2 (3 times). The mixture was maintained at 35 psi of H_2 pressure and was shaken on the parr. After 10 hours of reaction time TLC showed starting material was consumed. The solution was filtered through celite and the filtrate was concentrated under reduced pressure to give 585 mg of a tan foam. This crude amine was used without purification.

Step 2:

The crude amine (380 mg, 1.01 mmol) was dissolved into 2:1 acetone/H_2O and the solution was cooled to 0°C. Solid $NaHCO_3$ (170 mg, 2.02 mmol) was added

along with methyl chloroformate (119 mg, 1.26 mmol). The mixture was left to stir overnight with warming to room temperature. After 16 hours the reaction mixture was poured into a separatory funnel along with CH_2Cl_2. The mixture was washed with H_2O and brine. The organic phase was separated and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated to give a white foam that was purified by radial chromatography eluting with 20% $CH_3CN/CHCl_3$. This gave 367 mg of the title compound as a white foam (mixture of diastereomers). MP: 83-85°C. HRMS (EI) calcd for $C_{21}H_{27}FN_4O_5$ 434.1965, found 434.1971.

EXAMPLE 12: (*S*)-N-[[3-[3-fluoro-4-[*cis*-2-(acetoxyacetyl)-2,8-diazabicyclo[4.3.0]nonan-8-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

Step 1:

The crude amine intermediate described in EXAMPLE 11, Step 1, (500 mg, 1.33 mmol) was dissolved into 10 mL of dry CH_2Cl_2. The solution was cooled to 0°C and treated with 1.0 mL of dry pyridine followed by acetoxyacetyl chloride (218 mg, 1.59 mmol). This mixture was left to stir overnight with warming to room temperature. After 18 hours TLC showed starting material was consumed. The reaction mixture was poured into a separatory funnel along with CH_2Cl_2. The solution was washed with 0.5 N aqueous HCl, saturated aqueous $NaHCO_3$ and brine. The organic phase was separated and dried over anhydrous Na_2SO_4. Filtered and concentrated to give a gum that was purified by radial chromatography eluting with 10% CH_3CN/2% MeOH/$CHCl_3$. This gave 426 mg of the title compound as a white foamy solid (mixture of diastereomers). MP: 113-116°C. HRMS (EI) calcd for $C_{23}H_{29}FN_4O_6$ 476.2071, found 476.2065.

EXAMPLE 13: (*S*)-N-[[3-[3-fluoro-4-[*cis*-2-(hydroxyacetyl)-2,8-diazabicyclo[4.3.0]nonan-8-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

Step 1:

The starting material, EXAMPLE 12, (325 mg, 0.68 mmol) was dissolved into 6 mL of MeOH. The solution was cooled to 0°C under N_2. The solution was treated with 3.0 mL of 10% aqueous K_2CO_3. The mixture was stirred for 2 hours. After this time TLC showed U-141950 was consumed. The reaction was quenched with 1.0 N aqueous HCl to pH 6.5 (litmus). The reaction mixture was poured into a separatory funnel along with CH_2Cl_2. The solution was washed with H_2O and brine. The organic phase was separated and dried over anhydrous Na_2SO_4. Filtered and concentrated to give 276 mg of the title compound as a white foam

(mixture of diastereomers). MP: 102-110°C.

HRMS (EI) calcd for $C_{21}H_{27}FN_4O_5$ 434.1965, found 434.1975.

Following the general procedures outlined in the Charts and in view of the techniques used in the Examples 1-13, in particular to prepare (*S*)-N-[[3-[3-fluoro-4-[*cis*-3-(carbobenzyloxy)-3,7-diazabicyclo[3.3.0]octan-7-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (Example 1), (*S*)-N-[[3-[3-fluoro-4-[*cis*-3-(benzyloxyacetyl)-3,7-diazabicyclo[3.3.0]octan-7-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (Example 2); (*S*)-N-[[3-[3-fluoro-4-[*cis*-3-(hydroxyacetyl)-3,7-diazabicyclo[3.3.0]octan-7-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (Example 3); and (*S*)-N-[[3-[3-fluoro-4-[*cis*-3-(5-isoxazolinoyl)-3,7-diazabicyclo[3.3.0]octan-7-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (Example 4) the following additional compounds of Formula I can be prepared:

(*S*)-N-[[3-[3-fluoro-4-[*cis*-3-(acetoxyacetyl)-3,7-diazabicyclo[3.3.0]octan-7-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[*cis*-3-(formyl)-3,7-diazabicyclo[3.3.0]octan-7-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[*cis*-3-(methylsulfonyl)-3,7-diazabicyclo[3.3.0]octan-7-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[*cis*-3-(2-fluoroethyl)-3,7-diazabicyclo[3.3.0]octan-7-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[*cis*-3-(2-hydroxyethyl)-3,7-diazabicyclo[3.3.0]octan-7-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[*cis*-3-(2-methoxyethyl)-3,7-diazabicyclo[3.3.0]octan-7-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[*cis*-3-(cyanomethyl)-3,7-diazabicyclo[3.3.0]octan-7-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[*cis*-3-(carbomethoxy)-3,7-diazabicyclo[3.3.0]octan-7-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[(*S,S*)-2-(carbobenzyloxy)-2,8-diazabicyclo[4.3.0]non-8-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[(*S,S*)-2-(hydroxyacetyl)-2,8-diazabicyclo[4.3.0]non-8-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[(*S,S*)-2-(acetoxyacetyl)-2,8-diazabicyclo[4.3.0]non-8-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[(*S,S*)-2-(formyl)-2,8-diazabicyclo[4.3.0]non-8-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[(*S,S*)-2-(methylsulfonyl)-2,8-diazabicyclo[4.3.0]non-8-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[(*S,S*)-2-(2-fluoroethyl)-2,8-diazabicyclo[4.3.0]non-8-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[(*S,S*)-2-(2-hydroxyethyl)-2,8-diazabicyclo[4.3.0]non-8-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[(*S,S*)-2-(2-methoxyethyl)-2,8-diazabicyclo[4.3.0]non-8-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[(*S,S*)-2-(cyanomethyl)-2,8-diazabicyclo[4.3.0]non-8-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[(*S,S*)-2-(carbomethoxy)-2,8-diazabicyclo[4.3.0]non-8-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[(*R,R*)-2-(carbobenzyloxy)-2,8-diazabicyclo[4.3.0]non-8-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[(*R,R*)-2-(hydroxyacetyl)-2,8-diazabicyclo[4.3.0]non-8-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[(*R,R*)-2-(acetoxyacetyl)-2,8-diazabicyclo[4.3.0]non-8-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[(*R,R*)-2-(formyl)-2,8-diazabicyclo[4.3.0]non-8-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[(*R,R*)-2-(methylsulfonyl)-2,8-diazabicyclo[4.3.0]non-8-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[(*R,R*)-2-(2-fluoroethyl)-2,8-diazabicyclo[4.3.0]non-8-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[(*R,R*)-2-(2-hydroxyethyl)-2,8-diazabicyclo[4.3.0]non-8-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[(*R,R*)-2-(2-methoxyethyl)-2,8-diazabicyclo[4.3.0]non-8-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[(*R,R*)-2-(cyanomethyl)-2,8-diazabicyclo[4.3.0]non-8-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[(*R,R*)-2-(carbomethoxy)-2,8-diazabicyclo[4.3.0]non-8-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[*cis*-3-(carbobenzyloxy)-3,6-diazabicyclo[3.2.0]heptan-6-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[*cis*-3-(hydroxyacetyl)-3,6-diazabicyclo[3.2.0]heptan-6-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[*cis*-3-(acetoxyacetyl)-3,6-diazabicyclo[3.2.0]heptan-6-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[*cis*-3-(formyl)-3,6-diazabicyclo[3.2.0]heptan-6-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[*cis*-3-(methylsulfonyl)-3,6-diazabicyclo[3.2.0]heptan-6-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[*cis*-3-(2-fluoroethyl)-3,6-diazabicyclo[3.2.0]heptan-6-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[*cis*-3-(2-hydroxyethyl)-3,6-diazabicyclo[3.2.0]heptan-6-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[*cis*-3-(2-methoxyethyl)-3,6-diazabicyclo[3.2.0]heptan-6-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[*cis*-3-(cyanomethyl)-3,6-diazabicyclo[3.2.0]heptan-6-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[*cis*-3-(carbomethoxy)-3,6-diazabicyclo[3.2.0]heptan-6-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[*cis*-6-(carbobenzyloxy)-3,6-diazabicyclo[3.2.0]heptan-3-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[*cis*-6-(hydroxyacetyl)-3,6-diazabicyclo[3.2.0]heptan-3-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[*cis*-6-(acetoxyacetyl)-3,6-diazabicyclo[3.2.0]heptan-3-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[*cis*-6-(formyl)-3,6-diazabicyclo[3.2.0]heptan-3-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[*cis*-6-(methylsulfonyl)-3,6-diazabicyclo[3.2.0]heptan-3-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[*cis*-6-(2-fluoroethyl)-3,6-diazabicyclo[3.2.0]heptan-3-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[*cis*-6-(2-hydroxyethyl)-3,6-diazabicyclo[3.2.0]heptan-3-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[*cis*-6-(2-methoxyethyl)-3,6-diazabicyclo[3.2.0]heptan-3-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[*cis*-6-(cyanomethyl)-3,6-diazabicyclo[3.2.0]heptan-3-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[*cis*-6-(carbomethoxy)-3,6-diazabicyclo[3.2.0]heptan-3-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[*cis*-3-aza-6-oxobicyclo[3.2.0]heptan-3-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[*cis*-3-aza-6-(hydroxyimino)bicyclo[3.2.0]heptan-3-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[*cis*-3-aza-6-(methoxyimino)bicyclo[3.2.0]heptan-3-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[*cis*-3-aza-6-oxobicyclo[3.2.0]heptan-3-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide ethylene ketal;

(*S*)-N-[[3-[3-fluoro-4-[*trans*-3-aza-7-oxobicyclo[4.4.0]decan-3-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[*trans*-3-aza-7-(methoxyimino)bicyclo[4.4.0]decan-3-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[*trans*-3-aza-7-(hydroxyimino)bicyclo[4.4.0]decan-3-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[*trans*-3-aza-7-oxobicyclo[4.4.0]decan-3-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide ethylene ketal;

(*S*)-N-[[3-[3-fluoro-4-[*cis*-3-[2-(ethylsulfenyl)ethyl]-3,7-diazabicyclo[3.3.0]octan-7-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[*cis*-3-[2-[(4-morpholinyl)sulfonyl]ethyl]-3,7-diazabicyclo[3.3.0]octan-7-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[(*S,S*)-2-[2-(ethylsulfenyl)ethyl]-2,8-diazabicyclo[4.3.0]non-8-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[(*S,S*)-2-[2-[(4-morpholinyl)sulfonyl]ethyl]-2,8-diazabicyclo[4.3.0]non-8-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[(*R,R*)-2-[(4-morpholinyl)sulfonyl]ethyl]-2,8-diazabicyclo[4.3.0]non-8-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[(*R,R*)-2-[2-(ethylsulfenyl)ethyl]-2,8-diazabicyclo [4.3.0]non-8-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[*cis*-3-(2-fluorobenzoyl)-3,7-diazabicyclo[3.3.0]octan-7-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[*cis*-3-[(cyclopropyl)carbonyl]-3,7-diazabicyclo[3.3.0]octan-7-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[(*S,S*)-2-(2-fluorobenzoyl)-2,8-diazabicyclo[4.3.0]non-8-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[(*S,S*)-2-[(cyclopropyl)carbonyl]-2,8-diazabicyclo[4.3.0]non-8-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[(*R,R*)-2-(2-fluorobenzoyl)-2,8-diazabicyclo[4.3.0]non-8-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[(*R,R*)-2-[(cyclopropyl)carbonyl]-2,8-diazabicyclo[4.3.0]non-8-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[*cis*-3-(methoxyacetyl)-3,7-diazabicyclo[3.3.0]octan-7-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[*cis*-3-(methoxyacetyl)-3,7-diazabicyclo[3.3.0]octan-7-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[(*S,S*)-2-(methoxyacetyl)-2,8-diazabicyclo[4.3.0]non-8-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[(*S,S*)-2-(methoxyacetyl)-2,8-diazabicyclo[4.3.0]non-8-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[(*R,R*)-2-(methoxyacetyl)-2,8-diazabicyclo[4.3.0]non-8-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[(*R,R*)-2-(methoxyacetyl)-2,8-diazabicyclo[4.3.0]non-8-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

The following additional compounds of Formula II can be prepared using techniques of Formula I and as depicted in Chart VI:

(*S*)-N-[[3-[3-fluoro-4-[7-(hydroxyacetyl)-2,7-diazaspiro[4.4]nonan-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[7-(acetoxyacetyl)-2,7-diazaspiro[4.4]nonan-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[7-(formyl)-2,7-diazaspiro[4.4]nonan-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[7-(methylsulfonyl)-2,7-diazaspiro[4.4]nonan-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[7-(2-fluoroethyl)-2,7-diazaspiro[4.4]nonan-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[7-(cyanomethyl)-2,7-diazaspiro[4.4]nonan-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[7-(carbomethoxy)-2,7-diazaspiro[4.4]nonan-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[1-(hydroxyacetyl)-1,7-diazaspiro[4.4]nonan-7-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[1-(acetoxyacetyl)-1,7-diazaspiro[4.4]nonan-7-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[1-(formyl)-1,7-diazaspiro[4.4]nonan-7-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[1-(methylsulfonyl)-1,7-diazaspiro[4.4]nonan-7-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[1-(2-fluoroethyl)-1,7-diazaspiro[4.4]nonan-7-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[1-(cyanomethyl)-1,7-diazaspiro[4.4]nonan-7-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[1-(carbomethoxy)-1,7-diazaspiro[4.4]nonan-7-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[2-aza-7-oxospiro[4.5]decan-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[2-aza-7-(methoxyimino)spiro[4.5]decan-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-[2-aza-7-(hydroxyimino)spiro[4.5]decan-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide; and

(*S*)-N-[[3-[3-fluoro-4-[2-aza-7-oxospiro[4.5]decan-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide ethylene ketal.

Antibacterial Activity

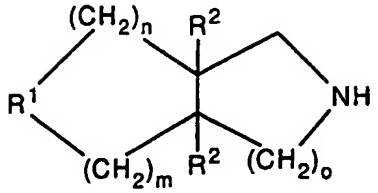
The oxazolidinone antibacterial agents of this invention have useful activity against a variety of organisms. The *in vitro* activity of compounds of this invention can be assessed by standard testing procedures such as the determination of minimum inhibitory concentration (MIC) by agar dilution as described in "Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically" (MFT) published Jan. 1983 by the National Committee for Clinical Laboratory Standards, 771 East Lancaster Avenue, Villanova, Pennsylvania 19084, USA. The activity of selected compounds of this invention against *Staphylococcus aureus* and *Streptococcus pneumoniae* are shown in Table 1.

Table 1

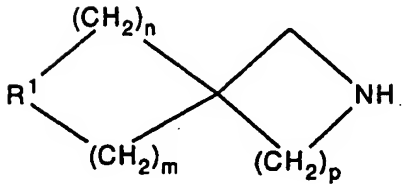
Minimum Inhibitory Concentration (μg/mL)

Example No.	*S. aureus* UC® 9213	*S. pneumoniae* UC® 9912
1	4	2
2	8	1
3	4	<0.5
vancomycin	1	0.5

Chart I



1



2

CHART II

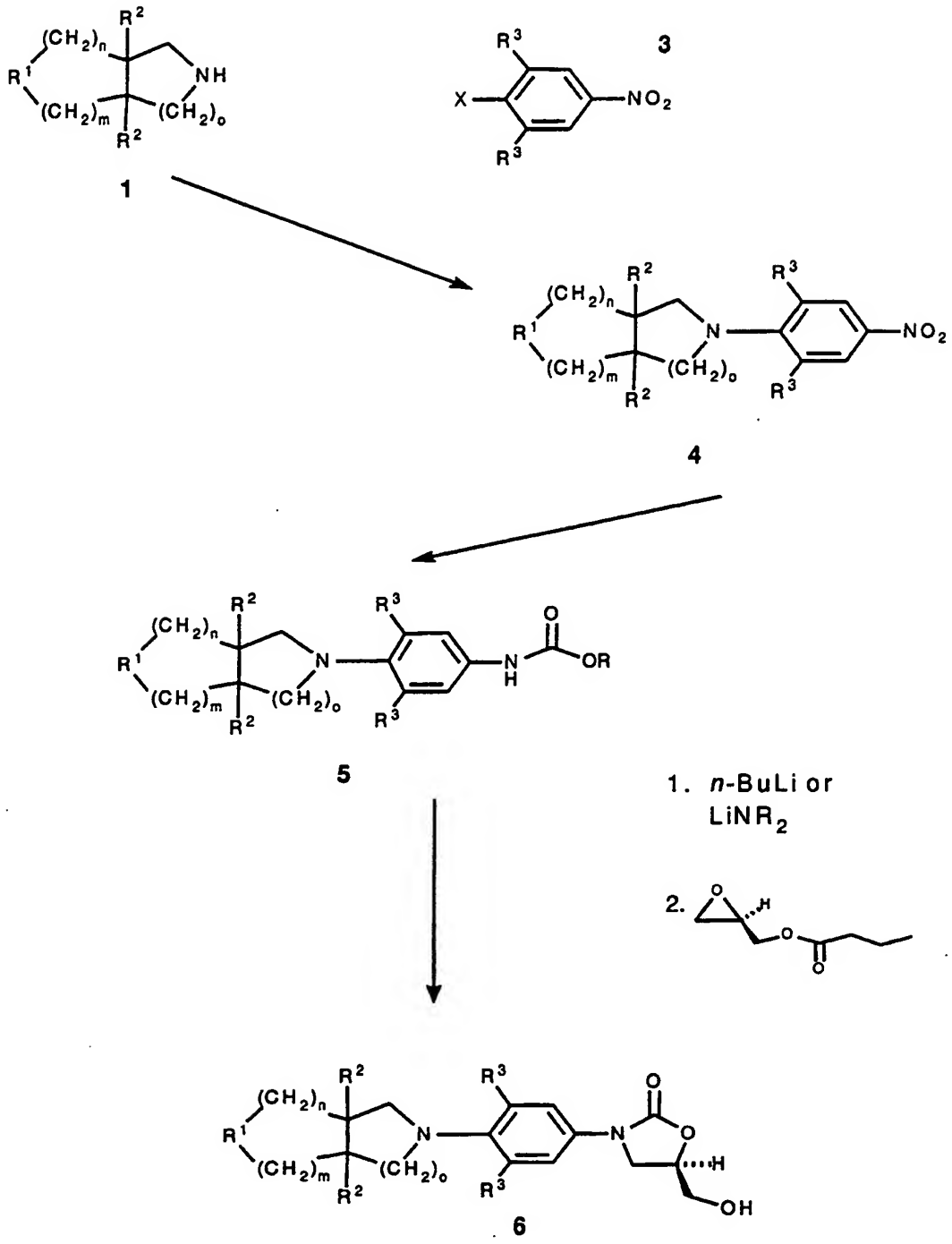


Chart III

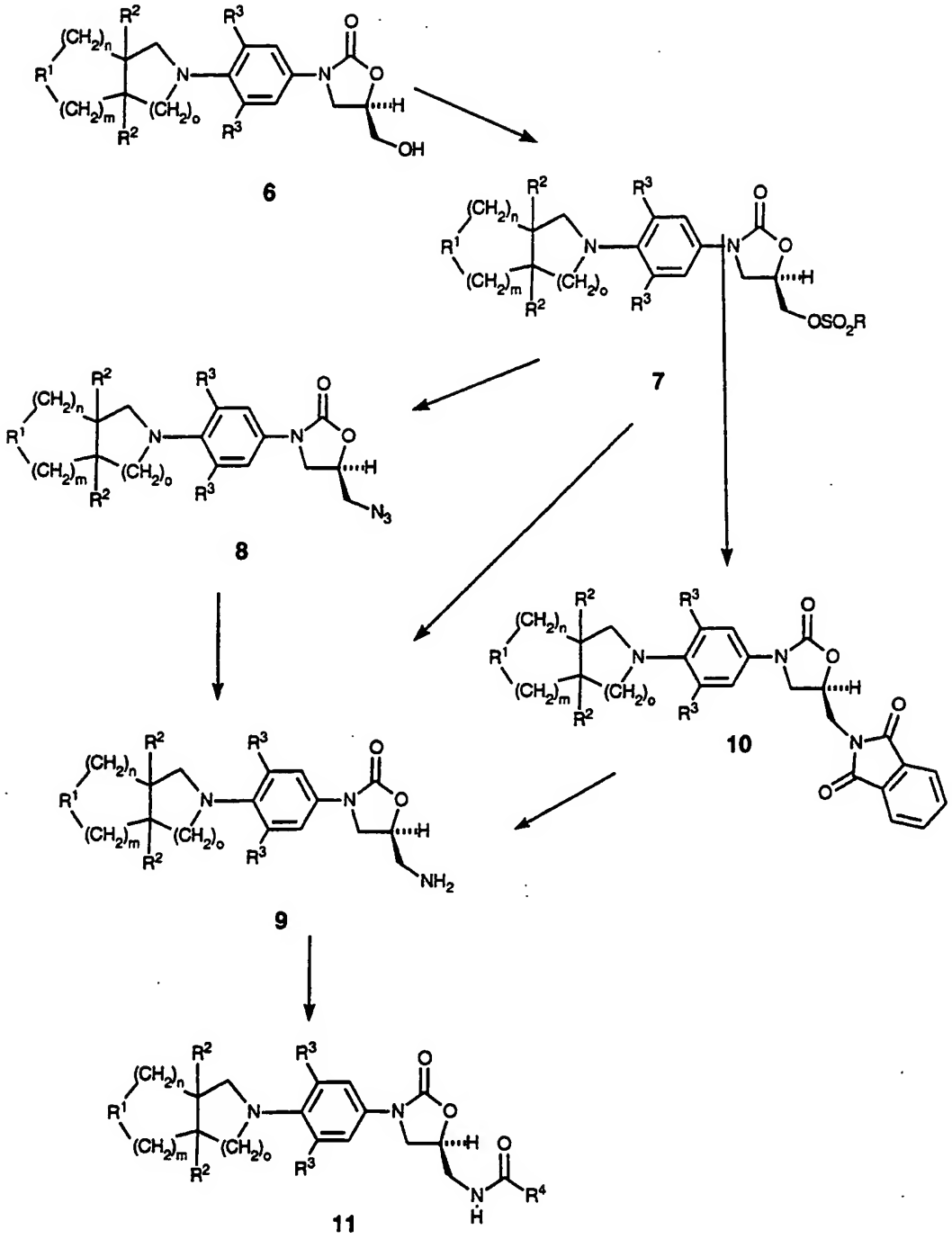


Chart IV

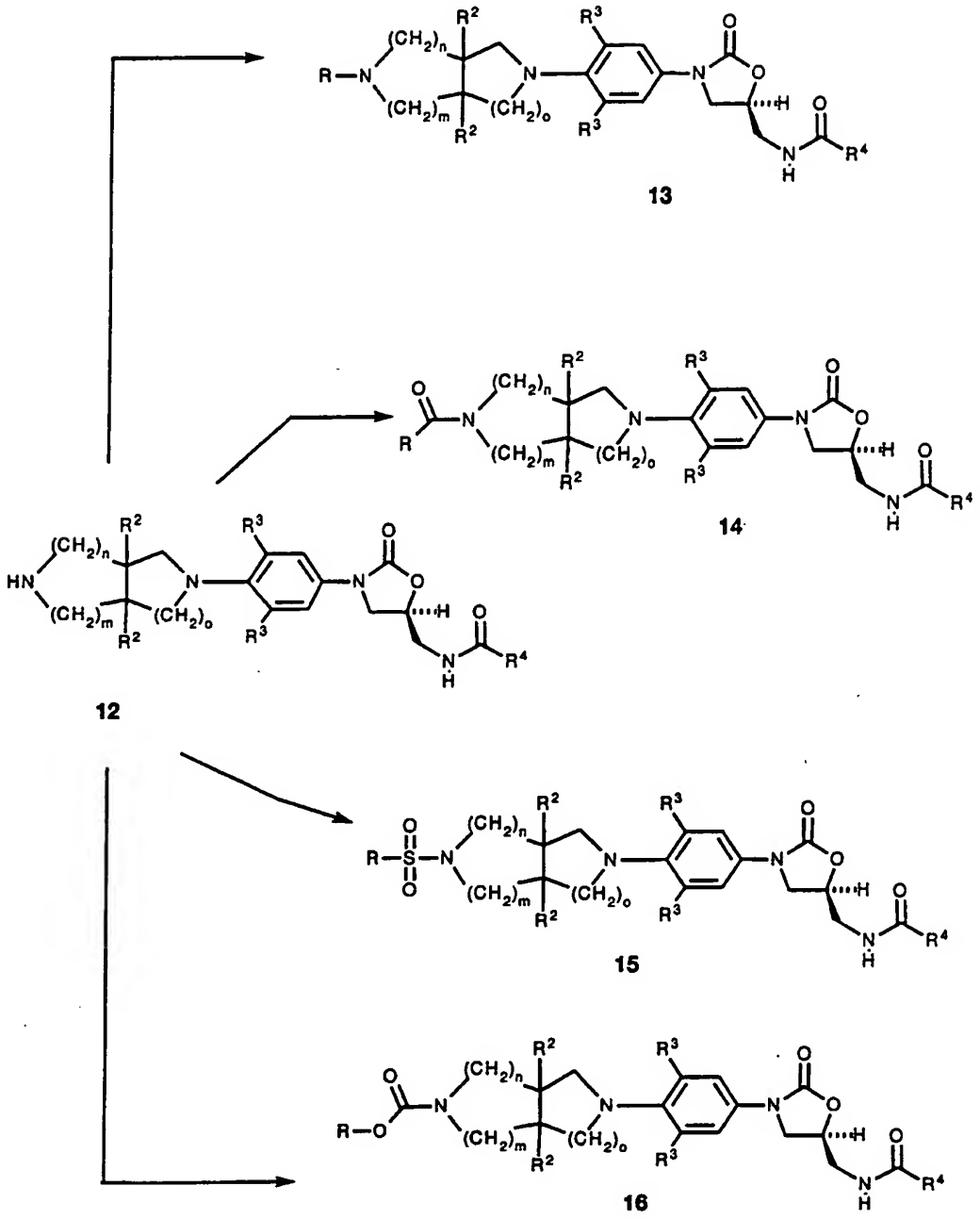


Chart V

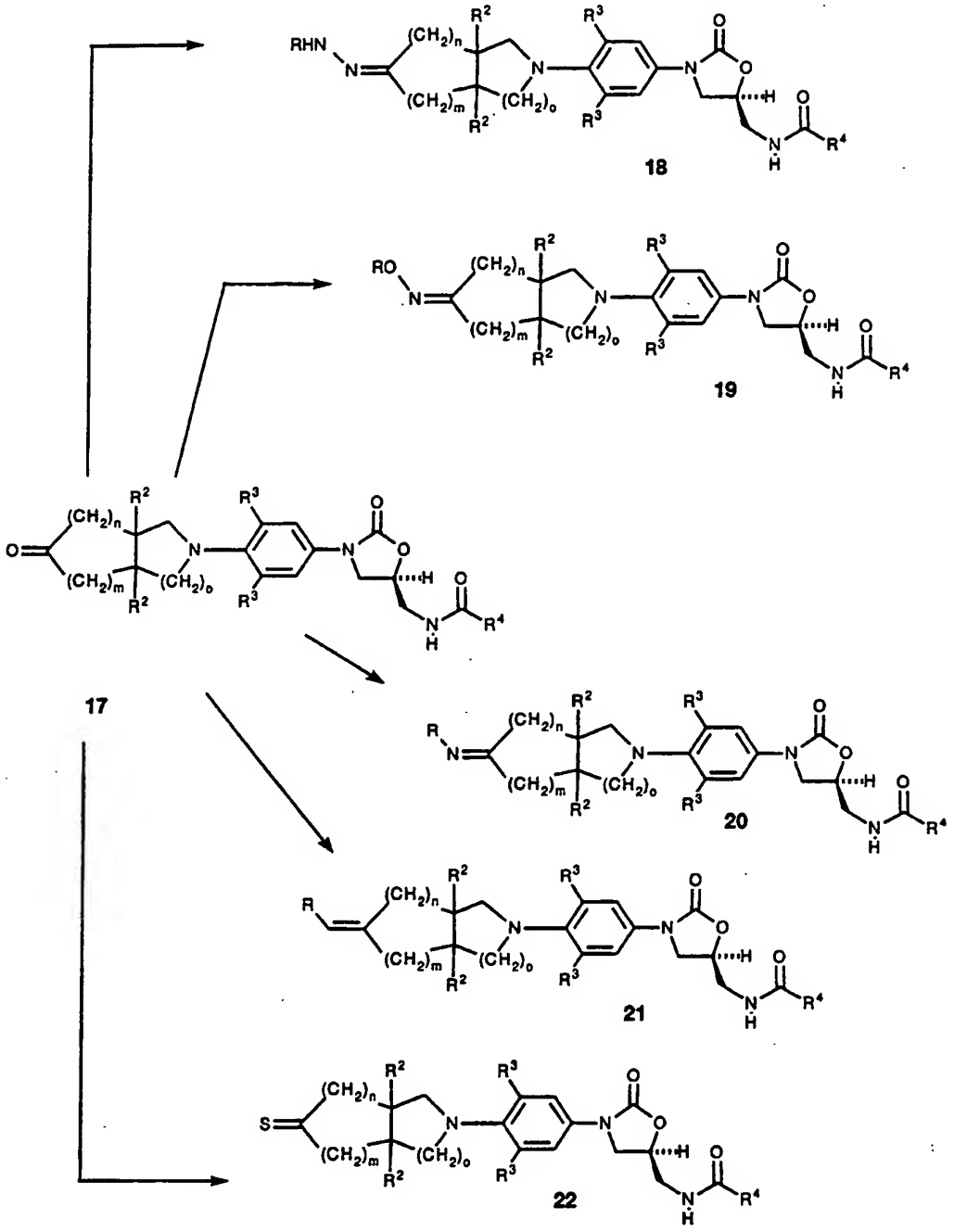
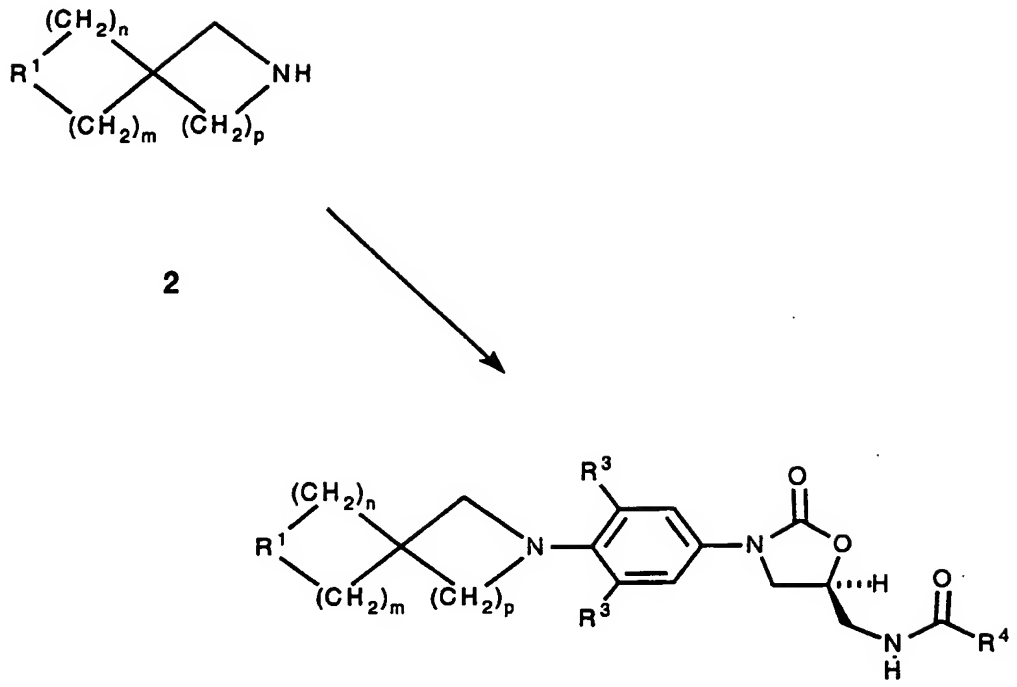


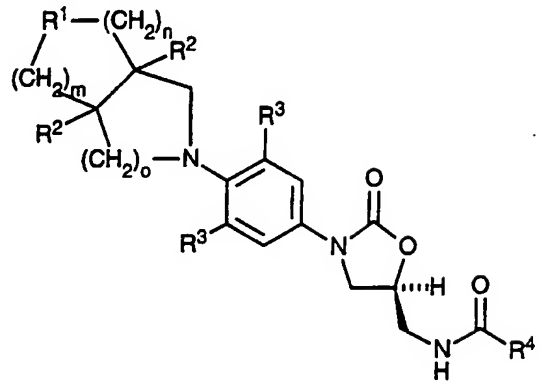
Chart VI



Formula II

What is Claimed:

1. A compound of structural Formula I:



Formula I

or pharmaceutically acceptable salts thereof wherein:

R^1 is (a) NR^5,

(b) CR^6R^7;

R^2 is independently H or CH_3;

R^3 is independently H, F, Cl or methoxy;

R^4 is (a) hydrogen,

(b) C_1-C_8 alkyl optionally substituted with one or more of the following: F, Cl, hydroxy, C_1-C_8 alkoxy, C_1-C_8 acyloxy,

(c) C_3-C_6 cycloalkyl,

(d) amino,

(e) C_1-C_8 alkylamino,

(f) C_1-C_8 dialkylamino,

(g) C_1-C_8 alkoxy;

R^5 is (a) H,

(b) C_{1-6} alkyl optionally substituted with one or more of the following: Cl, F, CN, OH, C_{1-4} alkoxy, amino, hydroxylamino, alkoxylamino, C_{1-4} acyloxy, C_{1-4} alkylsulfenyl, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, aminosulfonyl, C_{1-4} alkylaminosulfonyl, C_{1-4} dialkylaminosulfonyl, 4-morpholinylsulfonyl, phenyl (optionally substituted with one or more of F, Cl, CN, OH, C_1-C_4alkoxy), 5-isoxazolyl, ethenyloxy, ethynyl,

(c) C_{1-6} acyl optionally substituted with one or more of the following: Cl,

F, OH, SH, C_{1-4} alkoxy, naphthalenoxy and phenoxy (optionally substituted with one or more of the following: Cl, F, OH, C_1-C_4alkoxy, amino, C_1-C_4acylamino, C_1-C_4alkyl), amino, C_1-C_4acylamino, hydroxylamino, alkoxylamino, C_{1-4} acyloxy, phenyl, C_1-C_4alkylcarbonyl, C_1-C_4alkylamino, C_1-C_4dialkylamino, C_1-C_4hydroxyacyloxy, C_1-C_4alkylsulfenyl, phthalimido, maleimido, succinimido,

(d) C_{1-6} alkylsulfonyl optionally substituted with one or more of the following: Cl, F, OH, C_{1-4} alkoxy, amino, hydroxylamino, alkoxylamino, C_{1-4} acyloxy, phenyl,

(e) arylsulfonyl optionally substituted with one or more of the following: F, Cl, OCH_3, OH or C_{1-4} alkyl,

(f) C_{1-6} alkoxycarbonyl optionally substituted with one or more of the following: Cl, F, OH, C_{1-4} alkoxy, C_{1-4} acyloxy, phenyl,

(g) aminocarbonyl, C_{1-6} alkylaminocarbonyl or C_{1-6} dialkylaminocarbonyl (where the alkyl groups are optionally substituted with one or more of the following: Cl, F, OH, C_{1-4} alkoxy, phenyl),

(h) five- and six-membered heterocycles optionally substituted with one or more of the following: Cl, F, OH, amino, C_{1-4}acylamino, C_{1-4} alkylsulfonylamino, C_{1-4} alkoxycarbonylamino, C_{1-4} alkoxy, C_{1-4} acyloxy or C_{1-4}alkyl which can be substituted with F, OH or C_{1-4} alkoxy,

(i) C_3-C_6cycloalkylcarbonyl optionally substituted with one or more of the following: F, Cl, OH, C_1-C_4alkoxy, CN,

(j) benzoyl optionally substituted with one or more of the following: F, Cl, OH, C_1-C_4alkoxy, C_1-C_4alkyl, amino, C_1-C_4acylamino,

(k) pyrrolylcarbonyl optionally substituted with one or more of C_1-C_4alkyl,

(l) C_1-C_2 acyloxyacetyl where the acyl is optionally substituted with the following:
amino, C_1-C_4alkylamino, C_1-C_4dialkylamino, 4-morpholino, 4-aminophenyl, 4-(dialkylamino)phenyl, 4-(glycylamino)phenyl;

R^6 is (a) H,

(b) OH,

(c) C_{1-6} alkoxy,

(d) amino, C_{1-6} alkylamino, C_{1-6} dialkylamino, hydroxylamino, or

C_{1-2} alkoxylamino all of which can be optionally substituted on the nitrogen with: C_{1-6} acyl (optionally substituted with one or two of Cl or OH), C_{1-6} alkylsulfonyl optionally substituted with one or two of Cl or OH), or C_{1-6} alkoxycarbonyl,

(e) Cl or F;

R^7 is (a) H,

(b) C_{1-6} alkyl optionally substituted with one or more of the following: Cl, F, CN, OH, C_{1-4} alkoxy, C_{1-4} acyloxy, amino,

(c) CN,

(d) phenyl optionally substituted with one or more of the following: Cl, F, OH, C_{1-4} alkoxy; or

R^6 and R^7 taken together are (a) carbonyl or thiocarbonyl group,

(b) ethylene ketal ($-OCH_2CH_2O-$), propylene ketal ($-OCH_2CH_2CH_2O-$), ethylene thioketal ($-SCH_2CH_2S-$), propylene thioketal ($-SCH_2CH_2CH_2S-$), dimethyl ketal, diethyl ketal, dimethyl thioketal or diethyl thioketal,

(c) oxime optionally substituted with H, C_{1-6} alkyl (optionally substituted with Cl, F or C_{1-4} alkoxy), C_{1-6} acyl (optionally substituted with one or more of the following: Cl, F, OH, C_{1-4} alkoxy, C_{1-4} acyloxy),

(d) hydrazone optionally substituted with H, C_{1-6} alkyl (optionally substituted with one or more Cl, F, OH, C_{1-4} alkoxy, C_{1-4} acyloxy, phenyl, C_{1-6} acyl (optionally substituted with one or more of Cl, F, OH, C_{1-4} alkoxy, C_{1-4} acyloxy, phenyl), C_{1-6} alkoxycarbonyl (optionally substituted with one or more of the following: Cl, F, OH, C_{1-4} alkoxy, C_{1-4} acyloxy, phenyl), or C_{1-6} alkylsulfonyl,

(e) imine optionally substituted with H or a C_{1-6} alkyl (optionally substituted with Cl, F, OH, C_{1-4} alkoxy, C_{1-4} acyloxy, phenyl),

(f) carbon-carbon double bond optionally substituted with H, C_{1-4} alkoxycarbonyl, C_{1-4} alkyl (optionally substiuted with Cl, F, OH, C_{1-4} alkoxy, phenyl);

m is 0-2; n is 1-3; o is 0-3; and p is 1-3.

2. The compound of Claim 1 wherein one R^3 is fluorine and the other is hydrogen.

3. The compound of Claim 1 wherein each R^3 is fluorine.

4. The compound of Claim 1 wherein R^4 is hydrogen, methyl, difluoromethyl, dichloromethyl, hydroxymethyl or methoxy.

5. The compound of Claim 4 wherein R^4 is methyl, difluoromethyl, dichloromethyl or methoxy.

6. The compound of Claim 5 wherein R^4 is methyl.

7. The compound of Claim 1 wherein R^5 is hydroxyacetyl.

8. The compound of Claim 1 which is

(a) (*S*)-N-[[3-[3-fluoro-4-[*cis*-3-(carbobenzyloxy)-3,7-diazabicyclo[3.3.0]octan-7-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (Example 1),

(b) (*S*)-N-[[3-[3-fluoro-4-[*cis*-3-(benzyloxyacetyl)-3,7-diazabicyclo[3.3.0]octan-7-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (Example 2), or

(c) (*S*)-N-[[3-[3-fluoro-4-[*cis*-3-(hydroxyacetyl)-3,7-diazabicyclo[3.3.0]octan-7-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (Example 3),

(d) (*S*)-N-[[3-[3-fluoro-4-[*cis*-3-(5-isoxazolinoyl)-3,7-diazabicyclo[3.3.0]octan-7-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (Example 4),

(e) (*S*)-N-[[3-[3-fluoro-4-[*cis*-3-(2-indolylcarbonyl)-3,7-diazabicyclo[3.3.0]octan-7-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (Example 5),

(f) (*S*)-N-[[3-[3-fluoro-4-[*cis*-3-(carbomethoxy)-3,7-diazabicyclo[3.3.0]octan-7-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (Example 6),

(g) (*S*)-N-[[3-[3-fluoro-4-[*cis*-3-(formyl)-3,7-diazabicyclo[3.3.0]octan-7-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (Example 7),

(h) (*S*)-N-[[3-[3-fluoro-4-[*cis*-3-(acetyl)-3,7-diazabicyclo[3.3.0]octan-7-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (Example 8),

(i) (*S*)-N-[[3-[4-[*cis*-3-(carbobenzyloxy)-3,7-diazabicyclo[3.3.0]octan-7-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (Example 9),

(j) (*S*)-N-[[3-[3-fluoro-4-[*cis*-2-(carbobenzyloxy)-2,8-diazabicyclo[4.3.0]nonan-8-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (Example 10),

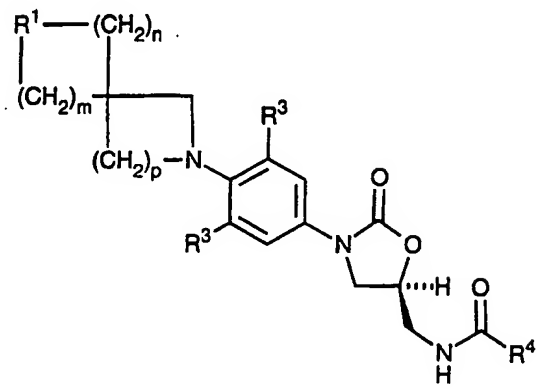
(k) (*S*)-N-[[3-[3-fluoro-4-[*cis*-2-(carbomethoxy)-2,8-diazabicyclo[4.3.0]nonan-8-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (Example 11),

(l) (*S*)-N-[[3-[3-fluoro-4-[*cis*-2-(acetoxyacetyl)-2,8-diazabicyclo[4.3.0]nonan-8-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (Example 12), or

(m) (*S*)-N-[[3-[3-fluoro-4-[*cis*-2-(hydroxyacetyl)-2,8-diazabicyclo[4.3.0]nonan-8-

yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (Example 13).

9. A compound of structural Formula II:



Formula II

or pharmaceutically acceptable salts thereof wherein:

R^1 is (a) NR^5,

(b) CR^6R^7;

R^2 is independently H or CH_3;

R^3 is independently H, F, Cl or methoxy;

R^4 is (a) hydrogen,

(b) C_1-C_8 alkyl optionally substituted with one or more of the following: F, Cl, hydroxy, C_1-C_8 alkoxy, C_1-C_8 acyloxy,

(c) C_3-C_6 cycloalkyl,

(d) amino,

(e) C_1-C_8 alkylamino,

(f) C_1-C_8 dialkylamino,

(g) C_1-C_8 alkoxy;

R^5 is (a) H,

(b) C_{1-6} alkyl optionally substituted with one or more of the following: Cl, F, CN, OH, C_{1-4} alkoxy, amino, hydroxylamino, alkoxylamino, C_{1-4} acyloxy, C_{1-4} alkylsulfenyl, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, aminosulfonyl, C_{1-4} alkylaminosulfonyl, C_{1-4} dialkylaminosulfonyl, 4-morpholinylsulfonyl, phenyl (optionally substituted with one or more of F, Cl, CN, OH, C_1-C_4alkoxy), 5-isoxazolyl, ethenyloxy, ethynyl,

(c) C_{1-6} acyl optionally substituted with one or more of the following: Cl, F, OH, SH, C_{1-4} alkoxy, naphthalenoxy and phenoxy (optionally substituted with one or more of the following: Cl, F, OH, C_1-C_4alkoxy, amino, C_1-C_4acylamino, C_1-C_4alkyl), amino, C_1-C_4acylamino, hydroxylamino, alkoxylamino, C_{1-4} acyloxy, phenyl, C_1-C_4alkylcarbonyl, C_1-C_4alkylamino, C_1-C_4dialkylamino, C_1-C_4hydroxyacyloxy, C_1-C_4alkylsulfenyl, phthalimido, maleimido, succinimido,

(d) C_{1-6} alkylsulfonyl optionally substituted with one or more of the following: Cl, F, OH, C_{1-4} alkoxy, amino, hydroxylamino, alkoxylamino, C_{1-4} acyloxy, phenyl,

(e) arylsulfonyl optionally substituted with one or more of the following: F, Cl, OCH_3, OH or C_{1-4} alkyl,

(f) C_{1-6} alkoxycarbonyl optionally substituted with one or more of the following: Cl, F, OH, C_{1-4} alkoxy, C_{1-4} acyloxy, phenyl,

(g) aminocarbonyl, C_{1-6} alkylaminocarbonyl or C_{1-6} dialkylaminocarbonyl (where the alkyl groups are optionally substituted with one or more of the following: Cl, F, OH, C_{1-4} alkoxy, phenyl),

(h) five- and six-membered heterocycles optionally substituted with one or more of the following: Cl, F, OH, amino, C_{1-4}acylamino, C_{1-4} alkylsulfonylamino, C_{1-4} alkoxycarbonylamino, C_{1-4} alkoxy, C_{1-4} acyloxy or C_{1-4}alkyl which can be substituted with F, OH or C_{1-4} alkoxy,

(i) C_3-C_6cycloalkylcarbonyl optionally substituted with one or more of the following: F, Cl, OH, C_1-C_4alkoxy, CN,

(j) benzoyl optionally substituted with one or more of the following: F, Cl, OH, C_1-C_4alkoxy, C_1-C_4alkyl, amino, C_1-C_4acylamino,

(k) pyrrolylcarbonyl optionally substituted with one or more of C_1-C_4alkyl,

(l) C_1-C_2 acyloxyacetyl where the acyl is optionally substituted with the following:
amino, C_1-C_4alkylamino, C_1-C_4dialkylamino, 4-morpholino, 4-aminophenyl, 4-(dialkylamino)phenyl, 4-(glycylamino)phenyl;

R^6 is (a) H,

(b) OH,

(c) C_{1-6} alkoxy,

(d) amino, C_{1-6} alkylamino, C_{1-6} dialkylamino, hydroxylamino, or C_{1-2} alkoxylamino all of which can be optionally substituted on the nitrogen with: C_{1-6} acyl (optionally substituted with one or two of Cl or OH), C_{1-6} alkylsulfonyl optionally substituted with one or two of Cl or OH), or C_{1-6} alkoxycarbonyl,

(e) Cl or F;

R^7 is (a) H,

(b) C_{1-6} alkyl optionally substituted with one or more of the following: Cl, F, CN, OH, C_{1-4} alkoxy, C_{1-4} acyloxy, amino,

(c) CN,

(d) phenyl optionally substituted with one or more of the following: Cl, F, OH, C_{1-4} alkoxy; or

R^6 and R^7 taken together are (a) carbonyl or thiocarbonyl group,

(b) ethylene ketal ($-OCH_2CH_2O-$), propylene ketal ($-OCH_2CH_2CH_2O-$), ethylene thioketal ($-SCH_2CH_2S-$), propylene thioketal ($-SCH_2CH_2CH_2S-$), dimethyl ketal, diethyl ketal, dimethyl thioketal or diethyl thioketal,

(c) oxime optionally substituted with H, C_{1-6} alkyl (optionally substituted with Cl, F or C_{1-4} alkoxy), C_{1-6} acyl (optionally substituted with one or more of the following: Cl, F, OH, C_{1-4} alkoxy, C_{1-4} acyloxy),

(d) hydrazone optionally substituted with H, C_{1-6} alkyl (optionally substituted with one or more Cl, F, OH, C_{1-4} alkoxy, C_{1-4} acyloxy, phenyl, C_{1-6} acyl (optionally substituted with one or more of Cl, F, OH, C_{1-4} alkoxy, C_{1-4} acyloxy, phenyl), C_{1-6} alkoxycarbonyl (optionally substituted with one or more of the following: Cl, F, OH, C_{1-4} alkoxy, C_{1-4} acyloxy, phenyl), or C_{1-6} alkylsulfonyl,

(e) imine optionally substituted with H or a C_{1-6} alkyl (optionally substituted with Cl, F, OH, C_{1-4} alkoxy, C_{1-4} acyloxy, phenyl),

(f) carbon-carbon double bond optionally substituted with H, C_{1-4} alkoxycarbonyl, C_{1-4} alkyl (optionally substiuted with Cl, F, OH, C_{1-4} alkoxy, phenyl);

m is 0-2; n is 1-3; o is 0-3; and p is 1-3.

10. The compound of Claim 9 wherein one R^3 is fluorine and the other is hydrogen.

11. The compound of Claim 9 wherein each R^3 is fluorine.

12. The compound of Claim 9 wherein R^4 is hydrogen, methyl, difluoromethyl, dichloromethyl, hydroxymethyl or methoxy.

13. The compound of Claim 12 wherein R^4 is methyl, difluoromethyl, dichloromethyl or methoxy.

14. The compound of Claim 13 wherein R^4 is methyl.

15. The compound of Claim 9 wherein R^5 is hydroxyacetyl.

16. A method for treating microbial infections in warm-blooded animals by administering to a patient in need thereof an effective amount of a compound of Formula I or II.

17. The method of Claim 16 wherein the compound of Formula I or II is administered in an effective amount of from about 0.1 to about 100 mg/kg of body weight/day.

18. The method of Claim 17 wherein the compound of Formula I or II is administered in an effective amount of from about 3.0 to about 50 mg/kg of body weight/day

INTERNATIONAL SEARCH REPORT

Inte: ;nal Application No
PCT/US 96/05202

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D487/04 A61K31/42 C07D471/04 C07D491/044 C07D491/052 C07D487/10 //(C07D471/04,221:00,221:00),(C07D487/04,209:00, 205:00),(C07D491/044,305:00,209:00),(C07D491/052,311:00,221:00),
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO,A,95 07271 (THE UPJOHN COMPANY) 16 March 1995 cited in the application see the whole document ---	1-18
Y	WO,A,93 09103 (THE UPJOHN COMPANY) 13 May 1993 cited in the application see the whole document ---	1-18
Y	WO,A,93 23384 (THE UPJOHN COMPANY) 25 November 1993 cited in the application see the whole document, especially page 5, lines 30-35 --- -/--	1-18

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
5 July 1996	24.07.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Scruton-Evans, I

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INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 96/05202

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 (C07D487/10,209:00,209:00),(C07D487/04,209:00,209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,Y	WO,A,95 25106 (THE UPJOHN COMPANY) 21 September 1995 see the whole document, especially the compound nos 30,56,58,61 and definitions of R4 and R5 ---	9
A	J. MED. CHEM, vol. 33, 1990, pages 2569-2578, XP002007586 W A GREGORY ET AL: "Antibacterials. Synthesis and structure-activity studies of 3-Aryl-2-oxooxazolidines" cited in the application see the whole document -----	1-18

☐ Further documents are listed in the continuation of box C.

[ ] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
	24.07.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter nal Application No
PCT/US 96/05202

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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		EP-A-	0610265	17-08-94
		JP-T-	7500603	19-01-95
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		CZ-A-	9402505	16-08-95
		EP-A-	0640077	01-03-95
		FI-A-	945246	08-11-94
		HU-A-	72296	29-04-96
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		SK-A-	133794	07-06-95
		ZA-A-	9302855	24-10-94
WO-A-9525106	21-09-95	JP-A-	8073455	19-03-96
		AU-B-	2099995	03-10-95